Questions and Answers About Gene Therapy

1. What are genes?

Genes are the biological units of heredity. Genes determine obvious traits, such as hair and eye color, as well as more subtle characteristics, such as the ability of the blood to carry oxygen. Complex traits, such as physical strength, may be shaped by the interaction of a number of different genes along with environmental influences.

A gene is part of a deoxyribonucleic acid (DNA) molecule. Humans have between 50,000 and 100,000 genes. Genes carry instructions that allow the cells to produce specific proteins such as enzymes. Only certain genes in a cell are active at any given moment. As cells mature, many genes become permanently inactive. The pattern of active and inactive genes in a cell and the resulting protein composition determine what kind of cell it is and what it can and cannot do. Flaws in genes can result in disease.

2. What is gene therapy and what are its objectives?

Advances in understanding and manipulating genes have set the stage for scientists to alter patients' genetic material to fight or prevent disease. Gene therapy is an experimental medical intervention that involves modifying the genetic material of living cells to fight disease.

Gene therapy is still experimental. It is being studied in clinical trials (research studies with humans) for many different types of cancer and for other diseases.

One of the goals of gene therapy is to supply cells with healthy copies of missing or altered genes. Instead of giving a patient a drug, doctors attempt to correct the problem by altering the genetic makeup of some of the patient's cells. Examples of diseases that could be treated this way include cystic fibrosis and hemophilia.

Gene therapy is also being studied as a way to change how a cell functions; for example, by stimulating immune system cells to attack cancer cells or by introducing resistance to human immunodeficiency virus (HIV), the virus that causes acquired immunodeficiency syndrome (AIDS).

3. How are genes transferred into cells so that gene therapy can take place?

In general, a gene cannot be directly inserted into a person's cell. It must be delivered to the cell using a carrier known as a "vector." The most common types of vectors used in gene therapy are viruses. Scientists use viruses because they have a unique ability to enter a cell's DNA. Viruses used as vectors in gene therapy are genetically disabled; they are unable to reproduce themselves.

Most gene therapy clinical trials rely on mouse retroviruses to deliver the desired gene. Other viruses used as vectors include adenoviruses, adeno-associated viruses, poxviruses, and the herpes virus.

4. What are retroviruses, and how can they be *safely* used in gene therapy?

Retroviruses contain ribonucleic acid (RNA) as their genetic material instead of DNA. Because retroviruses produce an enzyme called reverse transcriptase, they can transform their RNA into DNA, which becomes part of the DNA of the host cells.

There are many retroviruses. Retroviruses can cause AIDS and other diseases. In gene therapy, scientists inactivate certain retroviruses to prevent them from causing disease and to make them safe for use. This enables scientists to take advantage of the retroviruses' ability to deliver genes into the DNA of the host.

In addition to using retroviruses as the basis of treatment, researchers may also use a retrovirus to deliver a gene that makes cancer cells sensitive to an antibiotic. This technique can be used to stop a gene therapy experiment.

5. What are the basic steps involved in gene therapy?

In most gene therapy clinical trials, cells from the patient's blood or bone marrow are removed and grown in the laboratory. The cells are exposed to the virus that is carrying the desired gene. The virus enters the cells, and the desired gene becomes part of the cells' DNA. The cells grow in the laboratory and are then returned to the patient by injection into a vein. This type of gene therapy is called *ex vivo*, which means "outside the body." The gene is transferred into the patient's cells while the cells are outside the patient's body.

In other studies, vectors or liposomes (fatty particles) are used to deliver the desired gene to cells in the patient's body. This form of gene therapy is called *in vivo*, because the gene is transferred to cells inside the patient's body.

6. The first disease approved for treatment with gene therapy was adenosine deaminase (ADA) deficiency. What is this disease and why was it selected?

ADA deficiency is a rare genetic disease. The normal ADA gene produces an enzyme called adenosine deaminase that is essential for effective immune system function.

Patients with this condition do not have normal ADA genes, and their defective genes do not produce the functional ADA enzyme. ADA-deficient children are born with severe immunodeficiency and are prone to repeated serious infections, which may be life-threatening. Although ADA deficiency can be treated with a drug called PEG-ADA, the drug is expensive (more than $60,000 a year) and must be taken for life by injection into a vein.

ADA deficiency was selected for the first approved human gene therapy trial for several reasons:

- The disease is caused by a defect in a single gene, which increases the likelihood that gene therapy will succeed.

- The gene is regulated in a simple, "always on" fashion, unlike many genes whose regulation is complex.

- The amount of ADA present does not need to be precisely regulated. Even small amounts of the enzyme are known to be beneficial, while larger amounts are also tolerated well.

The first clinical trial of gene therapy began in September 1990. Two children diagnosed with ADA deficiency were treated with this new approach. As a precaution, they also continued to receive weekly doses of the drug PEG-ADA. The children's immune status improved after they received the gene therapy; however, it worked for only a few months and had to be repeated several times over the next 2 to 3 years. Since then, the children have had periodic tests which confirm that their re-engineered cells are surviving and producing the ADA enzyme. Both now take smaller doses of PEG-ADA to keep their disease under control.

7. How is gene therapy being studied in the treatment of cancer?

In studies of gene therapy for cancer, researchers are working to improve the body's natural ability to fight the disease or to make the cancer cells more sensitive to other kinds of treatment, such as chemotherapy. Some of the gene therapy techniques under study include:

- Substitution of a "working" copy of a gene for an inactive or defective gene. For example, this technique could be used to restore the ability of a defective gene (such as p53) to suppress or block the development of cancer cells.

- Injection of cancer cells with a gene that makes them more sensitive to treatment with an anticancer drug. Scientists hope that treatment with the drug will kill only the cells that contain the drug-sensitive gene.

- Introduction of the multidrug resistance (MDR) gene into stem cells (cells in the bone marrow that produce blood cells). The MDR gene is used to make the stem cells more resistant to the side effects of the high doses of anticancer drugs.

8. What risks are associated with current gene therapy trials?

Viruses can usually infect more than one type of cell. Thus, when viral vectors are used to carry genes into the body, they might alter more than the intended cells. Another danger is that the new gene might be inserted in the wrong location in the DNA, possibly causing cancer or other damage.

In addition, when DNA is injected directly into a tumor, or when a liposome delivery system is used, there is a slight chance that this DNA could unintentionally be introduced into reproductive cells, producing inheritable changes.

Other concerns include the possibility that transferred genes could be "overexpressed," producing so much of the missing protein as to be harmful; that the viral vector could cause inflammation or an immune reaction; and that the virus could be transmitted from the patient to other individuals or into the environment.

However, scientists use animal testing and other precautions to identify and avoid these risks before any clinical trials are conducted in humans.

9. What major problems must scientists overcome before gene therapy becomes a common technique for treating disease?

Scientists need to identify easier and better ways to deliver genes to the body. To treat cancer, AIDS, and other diseases effectively with gene therapy, researchers must develop vectors that can be injected directly into the patient. These vectors must then focus on appropriate target cells (such as cancer cells) throughout the body and successfully integrate the desired gene into the DNA of these cells.

Other advances that are needed include the ability to: deliver genes consistently to a precise location in the patient's DNA (thus diminishing the risk of causing cancer), and ensure that transplanted genes are precisely controlled by the body's normal physiologic signals.

Although scientists are working hard on these problems, it is impossible to predict when these obstacles will be overcome.

10. How do gene therapy trials receive approval?

A proposed gene therapy trial, or protocol, must be approved by at least two review boards at the scientists' institution. Gene therapy protocols must also be approved by the U.S. Food and Drug Administration (FDA), which regulates all gene therapy products. In addition, trials that are funded by the National Institutes of Health (NIH) must be registered with the NIH Recombinant DNA Advisory Committee (RAC). The NIH, which includes more than 20 institutes and offices, is the Federal focal point for biomedical research in the United States.

11. Why are there so many steps in this process?

Any studies involving humans must be reviewed with great care. Gene therapy in particular is a potentially very powerful technique, is relatively new, and could have profound implications. These factors make it necessary for scientists to take special precautions with gene therapy.

12. What are some of the social and ethical issues surrounding human gene therapy?

In large measure, the issues being confronted are the same ones that are faced whenever a powerful new technology is developed. Such technologies can accomplish great good, but they can also result in great harm if applied unwisely.

Gene therapy is currently focused on correcting genetic flaws and curing life-threatening disease, and regulations are in place for conducting these types of studies. But in the future, when the techniques of gene therapy have become simpler and more accessible, society will need to deal with more complex questions.

One such question is related to the possibility of genetically altering human eggs or sperm, the reproductive cells that pass genes on to future generations. (Because reproductive cells are also called germ cells, this type of gene therapy is referred to as germ-line therapy.) Another question is related to the potential for enhancing human capabilities—for example, improving memory and intelligence—by genetic intervention.

Although both germ-line gene therapy and genetic enhancement have the potential to produce benefits, possible problems with these procedures worry many scientists.

Germ-line gene therapy would forever change the genetic make-up of an individual's descendants. Thus, the human gene pool would be permanently affected. Although these changes would presumably be for the better, an error in technology or judgment could have far-reaching consequences. Germ-line gene therapy is not approved by the NIH.

In the case of genetic enhancement, there is anxiety that such manipulation could become a luxury available only to the rich and powerful. Some also fear that widespread use of this technology could lead to new definitions of "normal" that would exclude individuals

who are, for example, of merely average intelligence. And, justly or not, some people associate all genetic manipulation with past abuses of the concept of "eugenics," or the study of methods of improving genetic qualities through selective breeding.

13. What is being done to address these social and ethical issues?

Scientists working on the Human Genome Project, which is mapping and sequencing all of the human DNA, have recognized that the information gained from this work will have profound implications for individuals, families, and society. The Ethical, Legal, and Social Implications (ELSI) Program was established in 1990 to address these issues. The ELSI Program is designed to identify, analyze, and address the ethical, legal, and social implications of human genetics research at the same time that the basic scientific issues are being studied. In this way, problem areas can be identified and solutions developed before the scientific information becomes part of standard health care practice. More information about the Human Genome Project and the ELSI Program can be found on the National Human Genome Research Institute (NHGRI) Web site. The NHGRI Web site is located at http://www.nhgri.nih.gov on the Internet.

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Sources of National Cancer Institute Information

Cancer Information Service

Toll-free: 1–800–4–CANCER (1–800–422–6237)
TTY (for deaf and hard of hearing callers): 1–800–332–8615

NCI Online

Internet

Use http://cancer.gov to reach NCI's Web site.

CancerMail Service

To obtain a contents list, send e-mail to cancermail@icicc.nci.nih.gov with the word "help" in the body of the message.

CancerFax® fax on demand service

Dial 301–402–5874 and listen to recorded instructions.

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